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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/754,547	01/12/2004	Longgui Wang	15741.004	9273

7590 12/23/2008

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EXAMINER	
JAGOE, DONNA A	
ART UNIT	PAPER NUMBER
1614	
MAIL DATE	DELIVERY MODE
12/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/754,547	WANG ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,17-26,29 and 30* is/are pending in the application.

4a) Of the above claim(s) *21,23 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,17-20,22,24-26 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/7/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9, 17-26, 29 and 30 are pending in this application.

Claims 21, 23 and 30 are withdrawn.

Claims 1-9, 17-20, 22, 24-26 and 29 are rejected.

Applicants' arguments filed November 6, 2008 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 4, 5, 7-9, 17-20, 22, 24, 26 and 29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10, 14, 16, 17, 24-26, 32, 33, 35 and 36, of copending Application No. 11/104422. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and conflicting claims recite substantially the same subject matter, differing only in the recitation of the inhibition of proinflammatory cytokine expression in conflicting claim 1. Conflicting claims 10, 14, 16, 17, 24-26, 32, 33, 35 and 36 are fully encompassed by the instant claims because they are drawn to a method of treatment of treating ulcerative colitis. One skilled in the art would have been motivated to have interpreted the claims as broadly as is reasonable, and in doing so recognize that they are coextensive in scope and thus the proper subject of an obviousness-type double patenting rejection as outlined by *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 5, 7, 19-20 and 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eisenbrand et al. WO 00/61555 in view of Alternative Medicine Review (2002) and in further view of Drug Facts and Comparisons (1994) and the Merck Manual (U)

Eisenbrand et al. teach indirubin (reads on formula III of instant claim 1), indigo and isoindigo (each reads on formula II of instant claim 1) are natural products which

can be obtained from different plants, including Isatis tinctoria. Indigo naturalis is reported to have inter alia anti-inflammatory activity (page 1, lines 4-21). Eisenbrand et al. Alternative Medicine Review teaches that Isatis tinctoria is strongly inhibitory to the cyclooxygenase-2 enzyme and is theorized to be largely responsible for the anti-inflammatory action of Isatis (page 523). Inflammatory conditions are considered a major indication for Isatis leaf (page 524).

The Merck Manual teaches that Crohn's Disease is a chronic inflammation of the intestinal wall (lines 1-2, page 1).

Since both references identify the common problem of treating *Inflammation* with plants that contain indirubin and teaches that they have been well known to treat inflammatory conditions such as Crohn's disease or ulcerative colitis. Eisenbrand et al. gives specific example of a plant that carries indirubin, an isomer of indigo; the plant Isatis tinctoria, and Alternative Medicine Review teaches that Isatis tinctoria is a COX-2 inhibitor and is indicated for treatment of inflammatory conditions. It is therefore reasonable to conclude that the strength of correlation between references gives rise to reasonable expectation of success from combining them.

Regarding the combination of an analgesic/anti-inflammatory agent with the indirubin derivatives, Drug Facts and Comparisons teach analgesic agents (page 1210) such as ibuprofen and indomethacin are NSAIDs and routinely employed in the treatment of inflammatory diseases, such as rheumatoid arthritis (see chart, page 1211). As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980):

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. In re Susi, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); In re Crockett, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960). As this court explained in Crockett, the idea of combining them flows logically from their having been individually taught in the prior art.

While the recited inflammatory conditions are not specifically recited, it is prima facie obviousness to select a known material based on its suitability for its intended use, inflammation as recited by Alternative Medicine Review. See Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). Also, established precedent holds that it is generally obvious to add known ingredients to known compositions with the expectation of obtaining their known function. See, e.g., In re Linder, 457 F.2d 506, 507 (CCPA 1972); see also In re Dial, 326 F.2d 430,432 (CCPA 1964). Since the instantly claimed conditions such as inflammatory bowel disease and Crohn's disease are inflammatory conditions, it would have been obvious to employ the anti-inflammatory indirubin derivatives optionally combined with the instantly claimed well known anti-inflammatory agents because they are known to possess anti-inflammatory characteristics in the compositions of the primary reference.

Claims 1-9, 17-20, 22, 24-26 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kunikata et al (C3 from IDS dated August 15, 2005), Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenyujo EP 0 987 027 A1 (B1 from IDS dated August 15, 2005) and Drug Facts and Comparisons (1994) and in further view of Liu (C47 from IDS dated January 16, 2008).

Kunikata et al. teach *Polygonum tinctorium* is known to have the ability to suppress inflammation. The compounds indirubin (reads on formula II) and indigo (reads on formula I) were isolated from *P tinctorium* and exert an inhibitory effect on interferon-γ, which is a well-known inflammatory cytokine and also inhibits interleukin-6 (IL-6) production (see abstract). Kunikata states that the so-called inflammatory cytokines are induced in response to inflammatory stimuli. These inflammatory cytokines accelerate inflammatory reactions through activation of immunocompetent cells. Interferon γ, recited above, is thought to be a member of the inflammatory cytokine family (page 93, column 1 bridging to column 2). Kunikata isolated the active compounds indirubin and indigo (fig. 2, page 95) from P. tinctorium based on their ability to inhibit interferon-γ production (page 93 column 2). When tested it inhibited production of interleukin-6 in murine splenocytes (page 96, column 2).

Kunikata does not teach co-administration of other anti-inflammatory agents.

Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenyujo (hereinafter referred to as “Kabushiki”) teaches physiologically active extract of an indigo plant (see abstract) which exhibits anti-inflammatory effects (page 2 paragraph 0011). It is noted that the properties include controlling the production of cytokines including interferon-γ and interleukin 10 by immunocompetent cells. Treatment of conditions such as digestive diseases, Crohn's disease, Idiopathic ulcerative colitis, inflammation of pulmonary alveoli, multiple sclerosis, Alzheimer’s disease, etc. are recited on pages 5-6 paragraph 0023. It does not teach the concomitant administration of another anti-inflammatory agent.

Drug Facts and Comparisons teach analgesic agents (page 1210) such as ibuprofen and indomethacin are NSAIDs and routinely employed in the treatment of inflammatory diseases, such as rheumatoid arthritis (see chart, page 1211). One of ordinary skill in the art of the references listed above would have been a medical doctor with pharmaceutical or clinical research experience, or a chemist, biochemist, or a pharmacologist with a doctoral degree and with experience in the pharmaceutical industry, and either of which would also have had ability in identifying appropriate and acceptable combinations of active ingredients for commercial medications for symptoms of inflammation.

It would have been obvious to one having ordinary skill in the art to combine the anti-inflammatory agents indigo and indirubin as noted in Kunikata et al. and Kabushiki as noted above with anti inflammatory agents NSAIDs such as ibuprofen and indomethacin as noted in Drug Facts and Comparisons to treat inflammatory conditions, such Crohn's disease or ulcerative colitis with the reasoned expectation that it would reduce inflammation and the markers of inflammation, such as interleukin 6 and 10 as recited in Kunikata et al. and Kabushiki respectively. The combination of any of indirubin and indigo with any of the NSAIDs instantly claimed would have performed the same function as it did separately. One of ordinary skill in the art would have recognized that the results of the combination were predictable at the time the invention was made. The nature of the problem to be solved, treatment of inflammatory arthritis, as well as the need to increase efficacy of the overall treatment of inflammatory disease would have led one of ordinary skill in the art to combine the indigo derivatives of

Kunikata and Kabushiki together with the NSAIDs of Drug Facts and Comparisons. Therefore, it would have been obvious to treat inflammatory arthritis with indigo and indirubin combined with NSAIDs.

Regarding instant claim 3 and 22 drawn to an increase in solubility of the compound when at least R1 or R2 is in a group that increases solubility, Liu et al. teach that indirubin has poor solubility, poor absorption and irritation of the gastrointestinal tract and methylisoindigotin, abbreviated as meisoindigo (formula IV), a second generation derivative of indirubin exhibited higher activity than indirubin and less toxicity. The higher activity would indicate that the meisoindigo has a higher solubility over indirubin. Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious.

Regarding the administration of the indigo derivatives for inflammatory-related disease associated with cytokine expression levels, it would have been obvious to employ the recited indirubin and indigo compositions motivated by the teaching of Kunikata et al. and Kabushiki that indirubin and indigo exert anti-inflammatory, alleviation and detoxification actions (Kabushiki page 2 paragraph 11) by controlling the production of cytokines including interferon-γ and interleukin 10 by immunocompetent cells which relate to the determination of the balance between type 1 helper T-cells (Th1) and type 2 helper T-cells (Th2) to control the balance within the normal conditions and to treat/prevent the diseases such as autoimmune diseases (Kabushiki page 3, paragraph 0016). Inflammatory arthritis is an inflammatory related disease associated with cytokine levels.

Regarding claims 8 and 25, drawn to administration of at least two compounds administered concurrently or sequentially, the nature of the problem to be solved, treatment of inflammatory arthritis with an indigo derivative, would have led one of ordinary skill in the art to choose an appropriate carrier for the combination of two indigo derivatives to treat the symptoms of inflammatory arthritis administered together or in sequence. It would have been obvious to use a combination two indigo derivatives to lower toxicities by combining an optimal formulation of the indigo derivatives.

Since the instantly claimed conditions such as inflammatory bowel disease and Crohn's disease are inflammatory conditions, it would have been obvious to employ the anti-inflammatory indirubin derivatives optionally combined with the instantly claimed well known anti-inflammatory agents because they are known to possess anti-inflammatory characteristics in the compositions of the primary reference.

Response to Arguments

Applicant asserts that Eisenbrand et al. is directed to active substances that treat solid tumors and metastases and is not directed to the treatment Crohn's disease or ulcerative colitis. In response, Eisenbrand et al. Alternative Medicine Review teaches that Isatis tinctoria is strongly inhibitory to the cyclooxygenase-2 enzyme and is theorized to be largely responsible for the anti-inflammatory action of Isatis (page 523). Inflammatory conditions are considered a major indication for Isatis leaf (page 524). Applicant asserts that Eisenbrand fails to teach or suggest the administration of a compound of formula I, II, or III in an amount sufficient to treat the inflammatory related

disease by inhibiting pro-inflammatory cytokine expression or by stimulating anti-inflammatory cytokine expression but in an amount less than sufficient to substantially inhibit cyclin kinases as required by claim 1. In response, as noted in *In re Best* (195 USPQ 430 (CCPA 1977)), and *In re Fitzgerald* (205 USPQ 594 (CCPA 1980)), the mere recitation of newly-discovered function or property, inherently possessed by things in prior art, does not cause claims drawn to those things to distinguish over prior art. In such a situation, the burden is shifted to the applicant to prove that subject matter shown to be in prior art does not possess characteristic relied on where it has reason to believe that functional limitation asserted to be critical for establishing novelty in claimed subject matter may be inherent characteristic of prior art; whether rejection is based on "inherency" under 35 U.S.C. 102, on "prima facie obviousness" under 35 U.S.C. 103, jointly or alternatively, burden of proof is same. Applicant states that the Alternative Medicine Review article directed to Isatis tinctoria and its use as a COX-2 inhibitor in general which is not presently claimed. In response, it is well-known that COX-2 inhibitors directly targets COX-2, an enzyme responsible for inflammation and pain. Selectivity for *COX-2* reduces the risk of peptic ulceration. Further the compound Isatis tinctoria reads on the structure of formula II, currently claimed for the treatment of Crohn's disease or ulcerative colitis. It is prima facie obviousness to select a known material based on its suitability for its intended use, such as Isatis tinctoria with COX-2 selective inhibitory function to relieve inflammation without the risk of further peptic ulceration in Crohn's disease or ulcerative colitis. See Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Regarding the rejection of claims 1-9, 17-20, 22, 24-26 and 29 under 35 U.S.C. 103(a) as being unpatentable over Kunikata et al, Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenyujo EP 0 987 027 A1 and Drug Facts and Comparisons (1994) and in further view of Liu, Applicant states that the indirubin of Kunikata is employed only for TNCB induced delayed type hypersensitivity (allergic reaction). IN response, the allergic reaction is an inflammatory response. It would have been obvious to employ an agent, known to treat inflammation from an allergic reaction for treatment of inflammation of Crohn's disease or ulcerative colitis. Applicant alleges that " just because a compound inhibits IL-6, it does not necessarily mea' it would inhibit other pro-inflammatory cytokines necessary to treat chronic bowel disease as presently claimed. In response, the instant claims conflict with the prior art because the instant claims are also drawn to inhibition of IL-6, along with all other cytokines known. The claim elements appear in Kunikata in the same configurations (Polygonum tinctorium), serving the same functions (inhibit the cytokine IL-6), to achieve the results suggested in prior art to treat inflammation (Crohn's disease and ulcerative colitis are inflammatory diseases). Regarding the in vitro test, vs. in vivo, when there is motivation to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense". If there were a limited number of methods available, the skilled artisan would have had reason to try these methods, with the reasonable expectation that at least one would be successful.

Regarding Kabushiki, applicant asserts that along with the Polygonum tinctorium, the extract includes other agents. In response, the claim language *comprising* leaves the claim open for the inclusion of unspecified ingredients, even in major amounts. In response to applicant's arguments against the references individually, specifically to the Liu reference, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Liu is recited to show the obviousness of claims 3 and 22 drawn to an increase in solubility of the compound when at least R1 or R2 is in a group that increases solubility. Liu et al. teach that indirubin has poor solubility, poor absorption and irritation of the gastrointestinal tract and methylisoindigotin, abbreviated as meisoindigo (formula IV), a second generation derivative of indirubin exhibited higher activity than indirubin and less toxicity. The higher activity would indicate that the meisoindigo has a higher solubility over indirubin.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Donna Jagoe /D. J./
Examiner
Art Unit 1614

December 18, 2008

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614